REMARKS

The Rejection Under 35 U.S.C. § 112, First Paragraph for Lack of Written Description Should be Withdrawn

The Examiner has maintained the rejection of claims 84, 85, 87-91, 96-108 and 110 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner continues to assert that the claimed subject matter is not described in the specification in a way as to reasonably to convey to one skilled in the art that the inventors were in possession of the claimed invention at the time of filing.

Applicants traverse this rejection for all the reasons set out in the previous responses. To support these arguments, provided herewith is a Declaration of John Anderson, Ph.D. Under 37 C.F.R. 1.132 (denoted herein as the "Anderson Declaration"). In particular, the Anderson Declaration provides evidence demonstrating: (1) who would be one of ordinary skill in the art in relation to the present invention, (2) what the specification teaches from the viewpoint of one of ordinary skill in the art, (3) how one of ordinary skill in the art views the written description provided in Table 6, and (4) that the Applicants were in possession of the claimed subgenus at the time of filing. Furthermore, the Anderson Declaration discusses the support for the claimed subgenus in the specification and discusses the predictability of the invention in view of the art cited by the Examiner.

The pending claims are directed to methods of assaying for modulators of β-secretase activity using a substrate that comprises an APP molecule having a modified β-secretase processing site defined by the formula P_2P_1-$P_{1'}P_{2'}$, wherein: P_2 is N; P_1 is F; $P_{1'}$ is A and $P_{2'}$ s A. Thus, the claim-recited substrates are limited to those comprising a processing site of NFAA, and the claim further specifies that this processing site is a modification within an APP molecule. The number of members of the subgenus are therefore not overly broad, and as explained in our previous responses and the Anderson Declaration, it is clear to one of ordinary skill in the art that Applicants were in possession of the claim-recited substrates.

Applicants Intended to Claim Substrates having the Processing Site NFAA

The Examiner stated that the Applicants' support in the specification for the claim-recited substrate is, at best, a hind-sight selection of a particular sub-genus (see page 3

of the Office Action). Applicants traverse this characterization of the claimed invention As discussed in ¶C7 of the Anderson Declaration, Table 6 on page 30 of the specification provides a summary of the specific amino acids residues that are preferred at the cleavage site-proximal positions within a substrate, and it is clear to one of average skill that Table 6 illustrates that the Applicants contemplated substrates comprising the processing site of NFAA as recited in the current claims. In addition, Dr. Anderson stated that a person of average skill in the field of the invention would understand from Table 6 and its surrounding text that the inventors contemplated each of the permutations of $P_2P_1P_1{\cdot}P_2{\cdot}$ as defining an individual substrate (see ¶ C8). Table 6 is not a "laundry list" of "every possible moiety" as suggested in the action. Rather, it is a shorthand way of listing specific permutations that the inventors contemplated as the invention.

One of Ordinary Skill in the Art Would Expect the Claimed Methods to be Functional

The Examiner also stated that the art is too unpredictable for one to rely on the methods suggested by the Applicants and based on the species provided in the specification to expect the claimed subgenus will have the same activity as those exemplified in the specification (see page 3 of the Office Action). However, the claimed subgenus is a defined set of substrates that have been shown to be cleaved by β-secretase. As discussed in the Anderson Declaration and by the Applicants in previous responses (e.g. see page 10 of the Response dated December 5, 2006 and pages 11-12 of the Response dated February 29, 2008), International Patent Publication No. WO 02/094985 confirms that substrates having a core defined as P_2 is N; P_1 is F; P_1' is A; or P_2' is A, are cleaved 17 times more efficiently than the Swedish mutation. Evidence that the enzyme recited in the claims is able to cleave the substrate recited in the claims (NFAA) is certainly more probative than evidence cited by the Office that relates to other enzymes and/or other substrates.

Furthermore, the Anderson Declaration discusses support in the specification for the claimed subgenus of modified APP molecules comprising a modified *β*-secretase processing site defined as follows: P_2 is N; P_1 is F; P_1' is A; or P_2' is A (See ¶D2 – D6). As evinced by the Anderson Declaration, studies provided in the specification suggest that substrates comprising the elected amino acids at the core positions are likely cleaved by β-

secretase. This suggestion in the specification is confirmed by the post-filing dated provided in International Patent Publication No. WO 02/094982.

The Examiner continues to cite a number of references in order to illustrate the unpredictable state of the art: Gruninger-Leitch *et al.* (*J. Biol. Chem.,* 277:4687-4693, 2002), Majer *et al.* (*Protein Science* 6: 1458-1466, 1997), Sauder *et al.* (*J. Mol. Biol.,* 300:241-248, 2000), Shi *et al.* (*J. Alzheimer's Disease* 7: 139-148, 2005), and Tomasselli *et al.* (*J. Neurochem.,* 84:1006-1017, 2003). Furthermore, the Examiner states that the "Applicants' piecemeal analysis of the art does not overcome the objective consideration that one of ordinary skill in the art would develop regarding the art as a whole. Namely, that the art is largely unpredictable for one to rely on the methods suggested by Applicants based a few species to select either other species and expect the selected species to have the same activity." (See page 3 of the Office Action). The evidence presented herein should be more than sufficient where, as here, the evidence has the same core sequence NFAA as the core sequence recited in the claims. This is especially true where, as here, the claims specify that the core is inserted into an APP sequence, because APP is the known wild type substrate for the enzyme.

In Section E of the Anderson Declaration, Dr. Anderson comments on each of the cited references and provides evidence that the Examiner's analysis is flawed. Rather than supporting a theory of unpredictability, the Declaration states that the cited references, when viewed as whole, demonstrate that the vast majority of the peptide substrates disclosed in Table 6 of the patent application will be cleaved by β-secretase and the core amino acids are far more important to peptide cleavage as compared to residues at positions more distant from the cleavage site (see ¶E1-E6). In addition, the Anderson Declaration provides additional references demonstrating that the core residues are most important for substrate cleavability and a wide variety of sequences may be used as β-secretase substrates (see ¶E7-E9.) Therefore, the art cited by the Examiner provides evidence that the claimed subgenus of substrates is adequately supported by the specification. As already noted, for the particular claim set at issue in this case, residues that are more distant from the cleavage site are APP residues, and APP is the wild type substrate recognized by the enzyme. Thus, the evidence

presented by the Applicants is more probative than the evidence cited in the Office action in support of the rejection.

CONCLUSION

In view of the evidence provided in the Anderson Declaration and the above remarks, the claims satisfy the written description requirement and the rejection under 35 U.S.C. § 112, first paragraph should be withdrawn. Applicants believe pending claims 84, 85, 87-91, 96-108 and 110 are in condition for allowance. Applicants respectfully request reconsideration and withdrawal of all rejections and allowance of the claims currently under examination.

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Respectfully submitted,

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